REMARKS

Enablement Issue

The enablement rejection is limited to dependent claim 26, which read as follows:

> The method of claim 23 for quantitative assay of MASP-2 or MASP-2 activity in biological samples.

Base claim 23 in turn recites

> A method for detecting mannin-binding lectin associated serine protease-2 (MASP-2), said method
> (a) obtaining a biological sample;
>
> (b) contacting said biological sample with a MASP-2 polypeptide specific binding partner that specifically binds MASP-2, thereby forming complexes of said binding partner with said MASP-2 polypeptide, if any,; and
>
> (c) detecting said complexes of MASP-2 and said specific MASP-2 binding partner, if any, as an indication of the presence of mannin-binding lectin associated serine protease-2 in said sample,
>
> where said binding partner is an antibody according to claim 19.

Since base claim 23 recites detecting MASP-2, not necessarily MASP-2 activity, claim 26 was improper under 35 USC 112 ¶4. We have amended it to delete "or MASP-2 activity" to overcome this problem, which of course incidentally moots the enablement issue.

Applicants believe that they have enablement for a claim along the lines of, "The method of claim 23, further comprising detecting the enzymatic activity of said MASP-2 polypeptide in a sample". Note that this activity does not need to manifest itself <u>while</u> the MASP-2 is bound by the antibody of claim 19, that is, the MASP-2 can be released and <u>then</u> assayed for enzymatic activity. This meets the enablement argument set forth

in the paragraph bridging pp. 2-3 of the rejection.

Because this case is under final rejection, Applicants did not consider it prudent to present such a claim (if the Examiner thought it raised new issues, this entire amendment would have been refused entry). However, if the Examiner acknowledges the acceptability of the proposed claim, Applicants would like to present it.

2. Prior Art Issues

2.1. Claims 18-19, 22-23 and 40 stand rejected under 35 USC 102(a) as anticipated by Thiel et al. (Nature 386:606; 1997).

There are several issues:

(1) Are the rejected claims entitled to the priority date of the April 3, 1997 provisional application? If so, then Thiel et al. (1997), which the Examiner concedes was published the same day, is not prior art.

(2) Is the inventorship entity for the relevant disclosure in Thiel et al. (1997) the same as the inventorship entity for the rejected claims? If so, then Thiel et al. (1997) is not the disclosure of the "invention of another" as required by 35 USC §102(a).

Independent claims 18 and 19 were directed to:

> 18. An antibody produced by administering an antigen comprising a mannin-binding lectin associated serine protease-2 (MASP-2 polypeptide) to an antibody producing animal.
>
> 19. An antibody that specifically binds to MASP-2.

Claim 18 has been amended to limit it to antibodies raised against human MASP-2. New claim 44 limits 19 to antibodies which specifically bind human MASP-2. Spelling errors in claims 18 and 23 have been corrected.

2.2. In the present action, the Examiner contends that the "chicken antibody raised against a bovine lectin preparation"

does not satisfy the limitations of claim 18 because "it is not clear from the record that this 'bovine lectin preparation' is the same as an 'antigen comprising a mannan binding lectin associated serine protease-2' [MASP-2]".

Certainly, the antibody of claim 18 was not raised against human MASP-2. However, it appears to have been raised against bovine MASP-2, and claim 18 is not limited to human MASP-2.

The bovine lectin preparation in question was identified by P43, L17-18 as the one described in ref. 25 (Baatrup, et al., 1987), which is of record (reference "BM" in IDS). The bovine lectins and lectin-associated proteins were purified by zymosan affinity chromatography, gel permeation chromatography and SDS-PAGE.

The instant example 1 describes isolation of human MASP-2 from human plasma by a somewhat different procedure which included several carbohydrate affinity chromatography steps. The aforementioned anti-(bovine lectin preparation) chicken antibody recognized a 52 kDa protein band from the human isolate and the first 19 a.a. of the N-terminal were sequenced. The sequence was then used to raise the anti-N' MASP-2 antibody which the examiner concedes to recognize human MASP-2. This is persuasive evidence that the original chicken antibody was raised against a preparation containing the cognate bovine MASP-2 and in fact recognized the latter.

The chicken antibody in question thus satisfies claim 18 and its developers (Jensenius and Thiel) are the inventors of claim 18.

2.3. Turning to claims 19 and 23 the Examiner contends that since the chicken antibody was raised against a (presumably heterogeneous) bovine lectin preparation, it would not be expected to meet the "specifically binds" limitation.

Since, at present, applicants have no evidence as to the specificity of that chicken antibody, they are compelled to accept the Examiner's position (office action, p. 4, first full paragraph) that the first antibody satisfying the limitations of

claims 19 and 23 is the anti-N'-MASP-2 antibody referred to at P43, L22-26.

This antibody was raised against a 19 a.a. peptide corresponding to the first 19 a.a. of the human 52 kDa protein recognized by the anti-(bovine lectin preparation) antibody. The 52 kDa protein was sequenced by Anthony C. Willis, and the Examiner has taken the position (office action, p. 4, second full paragraph) that this sequencing was a "necessary inventive contribution" to claim 19.

Consequently, we have filed, on even date herewith, a request to correct inventorship to add Anthony C. Willis as an inventor. We assume that this request will be granted.

This means that vis-a-vis claim 19, Thiel et al. (1997) can no longer be considered to disclose the invention of "another". To the extent that it discloses antibodies which specifically bind MASP-2, it is disclosing the invention of the present inventors. Hence, it does not qualify as 102(a) prior art against claim 19.

2.4. With regard to the examiner's position concerning the inventorship of claim 40, this is moot as claim 40 has been cancelled. However, in cancelling claim 40, Applicants do not concede that the examiner's inventorship analysis is correct, they merely seek to narrow the issues in a case under final rejection.

While the Examiner did not specifically discuss claim 42, it too recites SEQ ID NO:2, and has been cancelled for the same reason (and with the same caveat).

2.5. In the May 27, 2003 office action, p. 4, the Examiner asserted that the provisional application is a verbatim copy of Thiel et al. (1997) (it isn't) and does not support the instant claims (it does). We are not sure whether the Examiner is still of this opinion, and hence address the issue here.

Reviewing the disclosure of the provisional application, we find disclosure of

(1) chicken antibody-raised against a bovine lectin

preparation recognized a human 52 kDa protein (MASP-2) as well as MBL (32 kDa).

(2) The 19 N-terminal AAs of this 52 kDa band were determined.

(3) A rabbit polyclonal antibody (anti-N'-MASP-2) was made against a peptide corresponding to the amino terminal (AAs 1-19) of the 52 kDa protein (MASP-2) and was shown to recognize a 52 kDa polypeptide and a 20 kDa polypeptide[1] (P43, L13-17; Fig. 1, lane 1.) (Ex. 1, P43, L13-17; P44, L9-10 and 18-22). This antibody was used in a Western blot (Ex. 3; P45, L19-21; P50, L10-12).

(4) The identities of 88 residues of MASP-2 (52 kDa band) were then determined directly.

(5) The complete AA sequence of MASP-2 was subsequently determined by cDNA sequencing; degenerate sense and antisense primers based on two known peptides (P46, L6-9).

(6) Chicken polyclonal antibody (anti-C' MASP-2) was raised against a mixture of two peptides corresponding, respectively, to AAs 505-523 and 538-556 in the C-terminal region of MASP-2 (Ex. 2; P44, L22-25). It recognized a 31 kDa polypeptide and a 76 kDa polypeptide (Ex. 1; P43, L28-P44, L4; Fig. 1, lines 3 and 4).

(7) The preparation of polyclonal and monoclonal antibodies against full-length MASP-2, or against other fragments of MASP-2 was suggested, but not then carried out. See P30, L26-P35, L19.

2.6. The Examiner asserted in the May 27, 2003 office

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[1] We consider the 20 kDa polypeptide, a truncated form, to be within the meaning of "a human MASP-2". See P4, L24-26. Thus, an antibody which binds both the 20 kDa and 52 kDa polypeptides still can be said to specifically bind human MASP-2.

action that "a mere disclosure of antisera against particular N and C terminal peptides cannot support claims to any kind of antibody against any portion of MASP-2" (para. bridging pp. 4-5).

This issue therefore reduces to whether it would have required undue experimentation to obtain antibodies against other epitopes of MASP-2 once a polyclonal antibody against the N-terminal epitope was available. The May 27, 2003 action assumed that the answer is negative, without any explicit review of the teachings of the specification or of the prior art.

It is unclear whether the Examiner still makes that assumption, so, in the interest of compact prosecution, we address that issue here.

Applicants do not contend that the preparation of antibodies against MASP-2 posed any special difficulties. The reason that their anti-(MASP-2) antibodies are novel is that applicants were the first to isolate MASP-2 itself (Prov. Appl. P3, L8-10).

As explained on P42, L23-P43, L13 of the provisional application, MASP-2 was isolated in sequenceable purity by a combination of (1) calcium-dependent mannan-sepharose affinity chromatography, (2) GlcNAc Sepharose affinity chromatography, and (3) preparative SDS-PAGE. The sequences of the amino terminal (41 amino acids) and of several tryptic fragments (27 a.a.; 12 a.a.; 8 a.a.) were determined; these are the sequences underlined in Fig. 6. See P48, L30-32.

Thus, it would have been easy to raise antibodies not only against MASP-2 (1-19), but also against the thus determined MASP-2 (20-41), MASP-2 (43-119), MASP-2 (362-373) and MASP-2 (395-402).

To raise antibodies against epitopes located elsewhere in MASP-2, it was not needful to know the complete AA sequence of MASP-2. All one needed was intact MASP-2 in a reasonably pure form. The procedure of Example 1 already provided MASP-2 in such form, and the anti-N'-MASP-2 antiserum could have been used to purify it further, if desired.

The techniques of making polyclonal and monoclonal

antibodies are well known in the art, and are indeed discussed in great detail at P30, L26-P35, L19.

We believe that the above disclosure, by itself, is sufficient to fully enable the claims.

Thus far, in analyzing the question of basis for the claims in the provisional application, we have ignored the disclosure of the complete amino acid sequence in Ex. 4 and Fig. 6. However, knowledge of this sequence allows one to (1) avoid purification of MASP-2 from plasma by instead producing MASP-2 recombinantly, and (2) predict the location of regions likely to be antigenic, "by criteria such as high frequency of charged residues", and of regions likely to contain epitopes unique to MASP-2, because they "lie outside of conserved regions". See P32, L31-P33, L1.

Thus, it is quite clear that even the provisional application (let alone the instant application) is fully enabling for the rejected claims.

Respectfully submitted,

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